

APPENDICES

APPENDIX I

SOLUTION TO TEACHING EXAMPLE

In the artificial example given in Section 4.4, tumours develop in six out of 15 animals in group 1 (control group), eight out of 15 in group 2 (low-dose group) and eight out of 15 in group 3 (high-dose group). We shall now outline the analysis of this example, using the methods given in Chapter 5.

- (a) Comparing these crude proportions according to Section 5.3 with option (3b) to choose the denominator, which leaves 14 animals at risk in group 3, results in no significant difference between any of the two groups and no significant trend with increasing dose levels (using scores 0, 1 and 2). The normal deviate of the Cochran-Armitage test for trend is 0.93 with a one-sided p -value of 0.176.
- (b) Using time-to-death information as available, but considering that all tumours were found in an incidental context, leads to a prevalence analysis for nonlethal occult tumours as described in Section 5.4. Separation of the time scale into ad-hoc runs (as illustrated in Table 5.4) leads in this case, to the following intervals with increasing prevalence:

[80, 80]:	0/1 = 0.00
[90, 120]:	2/7 = 0.29
[130, 180]:	14/26 = 0.54
[185, 200]:	6/11 = 0.55

From the resulting contingency tables, one derives the following observed and expected numbers of tumours in the three groups:

control group:	$O_0 = 6;$	$E_0 = 8.12$
low-dose group:	$O_1 = 8;$	$E_1 = 7.09$
high-dose group:	$O_2 = 8;$	$E_2 = 6.79$

The test for trend (again using scores 0, 1, 2) according to formula (5.4) gives $X_{PT}^2 = 1.61$, corresponding to a normal deviate $Z_{PT} = 1.27$, which leads to a one-sided p -value for positive trend of 0.102.

- (c) If one considers all tumours to be found in a fatal context, methods described in Section 5.5 for the analysis of rapidly lethal occult tumours and of observable tumours would be applied.

Table A.1 Analysis of artificial example using context of observation

Group	Tumours found in a fatal context		Tumours found in an incidental context		Combined	
	Observed	Expected	Observed	Expected	Observed	Expected
Control	2	4.64	4	5.17	6	9.81
Low-dose	3	3.10	5	3.84	8	6.95
High-dose	5	2.26	3	2.99	8	5.24

Observed and expected numbers are in this case:

$$\text{control group: } O_0 = 6; \quad E_0 = 10.26$$

$$\text{low-dose group: } O_1 = 8; \quad E_1 = 6.92$$

$$\text{high-dose group: } O_2 = 8; \quad E_2 = 4.82.$$

The test for positive trend according to formula (5.4) gives here $X_{PT}^2 = 4.55$, corresponding to a normal deviate $Z_{PT} = 2.13$, which results in a one-sided p -value for positive trend of 0.017.

- (d) Finally, making full use of the context of observation given in this data set, methods described in Section 5.6 would lead to the results summarized in Table A.1. Contexts coded 1 or 2 were considered as incidental tumours, and contexts 3 and 4 as fatal tumours. Animals with tumours found in the fatal context were not considered when computing the ad-hoc runs for the analysis of tumours found in an incidental context. The intervals are in this case: [80, 80], [100, 120], [130, 180], [200, 200].

Table A.1 gives the observed and expected numbers of tumours in the different contexts, both separately and combined. Calculating the trend statistic as described in Section 5.6 gives $X_{CT}^2 = 3.96$, corresponding to a normal deviate $Z_{CT} = 1.99$, which results in a one-sided p -value for positive trend of 0.024.

Without presenting a full survival analysis, it can be seen directly from the data in Table 4.4 that there is increasing mortality with increasing dose. Five animals in group 1 survive to 'terminal sacrifice' at time 200, three in group 2 and one in group 3. Correction for the difference in mortality is essential for an unbiased analysis. Considering all tumours to be found in a fatal context would overestimate the true effect, considering all tumours to be found in an incidental context would not lead to a significant trend, and the result considering contexts of observation lies between these two.